

Disease burden and its importance in patients with pemphigus

Doctoral dissertation

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1 Introduction

Pemphigus is a group of autoimmune bullous skin diseases encompassing potentially lethal conditions with a partly severe and chronic course, necessitating long-term treatment. Its most frequent subtype, pemphigus vulgaris (PV), accounts for 70-90% of cases and has an annual incidence of 0.76 to 32 per million. Other less frequent subtypes are pemphigus foliaceus (PF) and IgA pemphigus. Blister formation in pemphigus is caused by autoantibodies against cell-surface proteins of keratinocytes.

Both mucocutaneous symptoms and chronic immunosuppressive therapy may have a detrimental impact on patients' life. Treatment of pemphigus and the necessary health technologies additionally pose a significant burden on health systems and healthcare financing.

In the 1990s, the World Health Organization, the World Bank and Harvard School of Public Health together coined the concept of disease burden in order to describe and quantify death or health loss linked to a particular disease. Besides loss of function and mortality, disease burden also encompasses both impairment in health-related quality of life (HRQoL) and cost of illness. The latter two are constantly gaining importance due to the emerging prevalence of chronic diseases. Measuring disease burden has important clinical and health economic benefits for both the individual and society. Therapy may improve symptoms alone or HRQoL too; this distinction being not indifferent from taking into account the various economic effects of improving HRQoL. The assessment of HRQoL further allows to identify and then improve the most affected dimensions of HRQoL, thus personalizing medical care. Thorough recognition of the burden of a particular disease may additionally help clinicians to better understand patients' experience and optimize their management. There is an

increasing relevance of measuring HRQoL as novel, efficient therapeutic regimens for the management of pemphigus are expected to be introduced in near future. Cost-effectiveness analyses of these therapies require such HRQoL data. For instance, an important milestone of 2018 was rituximab being granted approval as a first-line monotherapy for PV by the Food and Drug Administration.

Analysing the cost of an illness aims to measure its economic burden from specific perspectives. The underlying concept is the assumption that a total cost of an illness equals the economic benefits of its complete healing. Costs of diseases can be divided into direct and indirect costs, the former encompassing direct medical and direct non-medical costs. Direct medical costs are the costs of resources directly linked to medical care (e.g. outpatient or inpatient care, treatment). Direct non-medical costs are linked to the disease itself but necessitate non-medical resources (e.g. travelling, non-medical care). Indirect costs are the economic consequence of diminished work productivity caused by the disease. Here, the distinction between presenteeism and absenteeism can be made. The former stands for not entirely diminished work productivity, the latter for the inability of working.

Only few studies have investigated and reported on the HRQoL impairment and costs of pemphigus. My thesis presents the results of a cross-sectional study investigating two important components of disease burden, namely HRQoL and cost of illness among Hungarian patients with pemphigus.

2 Aims

Our aims were:

- I. The assessment of health status and HRQoL in patients with pemphigus in Hungary.
 - a. Applying EQ-5D, a general questionnaire, for measuring pemphigus patients' HRQoL.
 - b. Identifying the most affected dimensions of health in pemphigus and factors influencing HRQoL.
 - c. Investigating feasibility and validity of EQ-5D in pemphigus patients.
 - d. Estimating health utility scores in pemphigus.
- II. Measuring costs of pemphigus in Hungary.
 - a. Quantifying direct medical, direct non-medical and indirect costs of pemphigus.
 - b. Identifying the largest cost categories.

3 Methods

Between December 2014 and June 2017, a cross-sectional study was conducted in four academic dermatology departments in Hungary. Consecutive patients over 18 years of age diagnosed with any form of pemphigus were enrolled after an informed consent form was read and signed. Permission for conducting the study was granted by the National Scientific and Ethical Committee (reference No. ETT-TUKÉB 27416-3/2016/EKU). The questionnaire consisted of two sections. The patients' section included questions regarding demographic data, comorbidities and HRQoL. The latter was examined by the validated Hungarian versions of standard outcome measures [DLQI (Dermatology Life Quality Index), EQ-5D (5-level EuroQol-5D)]. Physicians' section contained questions referring to disease characteristics, medical history, disease severity [ABSIS (Autoimmune Bullous Skin Disorder Intensity Score)] and treatments applied.

3.1 EQ-5D

EQ-5D is a generic, self-reported, preference-based measure of health that consists of a five-item descriptive system and a visual analogue scale (EQ VAS). The five dimensions of health ask about mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five response levels (1-no problems, 2-slight problems, 3-moderate problems, 4-severe problems, 5-extreme problems/unable) and the different combinations of answers define $5^5=3125$ distinct health states. Each health state can be assigned a utility value (i.e. EQ-5D-5L index score) ranging between -0.285 and 1 (1 equals complete health, 0 equals death, negative values equal conditions considered worse than death) obtained from population studies reflecting the societal values. EQ VAS is a 20-cm-long, vertical visual analogue scale with endpoints of '0'

(‘The worst health you can imagine’) and ‘100’ (‘The best health you can imagine’). It provides a self-rating of patients’ current health status.

EQ-5D being a generic measure of health allows to compare multiple diseases to each other as well as to general population reference values. Validity and sensitivity of EQ-5D have already been confirmed in several dermatological conditions (e.g. psoriasis, atopic dermatitis, hidradenitis suppurativa, acne vulgaris). EQ-5D is commonly used in cost-effectiveness studies for health utility calculations.

3.2 DLQI

DLQI is the most frequently employed tool for measuring dermatology-specific HRQoL both in general dermatology and in pemphigus patients. Its psychometric properties have been verified in more than 110 studies with excellent results regarding validity, sensitivity and reliability. The ten-item questionnaire covers the commonly mentioned aspects of life affected by skin disease: symptoms and feelings, daily activities, leisure, school and work, personal relationships, and treatments. Each dimension has four possible answers (0-not at all/not relevant, 1-a little, 2-a lot, 3-very much). The DLQI has a possible scoring range of 0–30, with ‘30’ corresponding to the worst, and ‘0’ corresponding to the best score.

3.3 ABSIS

ABSIS is the validated severity measure of bullous skin diseases. The various presentation of pemphigus necessitated a scoring system that quantifies even small changes in disease severity thus enabling to compare efficacy of various treatments.

The ABSIS score ranges between 0-206, its first part describes the degree of body surface area (BSA) involvement by skin

symptoms according to the Wallace rule of nines. This skin severity sub-score may reach a maximum of 150 in multiplying BSA with a weighing factor of skin symptom quality: 1.5 for erosions or exudative lesions, 1.0 for crusted lesions and 0.5 for re-epithelialized or healed symptoms. The second sub-score stands for degree (0-11) and severity (0-45) of oral mucous membrane symptoms, the latter being valued according to subjective complaints during eating or drinking.

3.4 Global and pain assessments

To assess disease severity, the Physicians' Global Assessment (PGA) VAS and Patient's Global Assessment (PtGA) VAS were administered, both providing a range of scores from 0-100, where 0 indicated 'not severe at all' and 100 represented 'very severe'. The average and worst pemphigus-related pain intensities experienced by the patients in the past three months were recorded on a 100-point, horizontal VAS with the endpoints of 'no pain at all' (=0) and 'pain as bad as it could be' (=100).

3.5 Cost calculation

Disease costs have been calculated retrospectively for the preceding 12 months. A societal perspective was adopted, and prices were expressed in HUF (2017). Data of resource utilization were collected in our questionnaire's patient and physician sections. The number of outpatient GP and dermatological visits and inpatient care was collected. We gathered data on patients' medication and travel costs, informal care received from friends or family, social or paid care and productivity loss caused by pemphigus. The latter was evaluated with the Work Productivity and Activity Impairment (WPAI) questionnaire where data was collected on time spent at work in the preceding one week and time span of not being

able to work due to the disease itself. The degree of how much pemphigus influenced work productivity was assessed on a VAS ranging between 0-10 with 0 for 'not at all' and 10 for 'complete inability to work'.

4 Results

4.1 Patient characteristics

In total, 109 pemphigus patients participated in the study. Mean age was 57.2 ± 14.8 (range 19-93) years, and 64.2% were males. The proportion of patients with full-time employment was 37.6%, 34.9% was over the retirement age, whereas 13.8% disability pensioner. Mean disease duration was 3.8 ± 4.9 years. The most frequently represented subtype was PV (n=81), whereas 27 patients were presented with PF, and one patient had IgA pemphigus. At the time of the survey, the majority of patients were symptom-free, 26 patients (23.9%) had mucous membrane symptoms, 25 patients (22.9%) presented with skin-only symptoms. Nearly two-thirds of the patients previously had concomitant mucocutaneous symptoms during their disease course.

Based on ABSIS scores, 47.2% of patients had limited pemphigus, 46.8% moderate or severe pemphigus. Only five patients had an extreme severity.

At the time of the survey, the most commonly used treatments were systemic corticosteroid therapy (70.6%), azathioprine (42.2%) and cyclophosphamide (10.1%) (combinations occurred). Only 10 patients received topical therapy, while three had no treatment at all.

The most frequent comorbidities in patients were as follows: 21 patients (18.5%) had no concomitant disease at the time of the survey, 26-26 patients (24.7%) had at least one or two known medical conditions and 17 patients (15.6%) had four or more comorbidities. Half of the patients had hypertension, a quarter had hyperlipidaemia. Osteoporosis or musculoskeletal disease was known in 41 patients (37.6%).

4.2 General and dermatology-specific HRQoL results (EQ-5D, DLQI)

Overall, 50%, 43%, 43%, 42% and 19% of the pemphigus patients reported problems in pain/discomfort, mobility, anxiety/depression, usual activities and self-care dimensions of the EQ-5D descriptive system, respectively. Mean EQ-5D index and EQ VAS scores were 0.82 ± 0.21 and 68.0 ± 22.3 , respectively. Four percent of the patients reported pain/discomfort caused by pemphigus to be severe. The most patients reported at least moderate or worse problems in this same dimension. Mobility and anxiety/depression posed problems to some extent in 43-43% of the patients.

Sixty different EQ-5D health states occurred among the patients. The best health state (11111) was indicated by 31 patients (28.7%); thus, a substantial ceiling effect of the EQ-5D descriptive system was detected. The second most common health state was 11112, indicated by 8 patients (7.3%) and the third were 11121 and 31111 with 4-4 patients (3.7%). No negative EQ-5D index scores were observed (i.e. health states being worse than dead).

Mean DLQI score was 5.4 ± 6.9 , with the most problems reported regarding sore, itchy or painful skin (48%), embarrassment (48%) and clothing (36%). Overall, 40 patients (37.4%) had a DLQI total score of zero.

4.3 Comparison of PV and PF patients

ABSIS scores showed a trend toward higher severity score in PV compared with PF. Patients affected by PV tended to have worse scores both in EQ-5D index (0.81 ± 0.22 vs. 0.86 ± 0.20) and EQ VAS (67.6 ± 23.6 vs. 69.7 ± 18.6) with the difference being not significant ($p=0.142$ and $p=0.937$). However, PF

patients experienced greater although not significant HRQoL impairment as measured with the DLQI ($p=0.279$).

4.4 Validity of EQ-5D

EQ-5D index scores demonstrated a strong correlation with DLQI and EQ VAS scores, a moderate-to-strong correlation with average pain intensity VAS and a moderate correlation with ABSIS, PGA VAS, PtGA VAS and worst pain intensity VAS scores ($p<0.001$). In contrast, EQ VAS moderately correlated with the DLQI and the scores on pain intensity scales ($p<0.001$). There was a weak, insignificant correlation between EQ VAS and ABSIS scores. PGA VAS highly correlated with both the DLQI and ABSIS ($p<0.001$). A weak negative correlation was found between age and both the EQ-5D index scores ($p<0.01$) and the EQ VAS ($p<0.05$).

There was no statistically significant difference in EQ-5D index scores between females and males. Mean EQ-5D index scores of patients with limited, moderate, severe and extreme disease were 0.88 ± 0.18 , 0.82 ± 0.21 , 0.72 ± 0.23 and 0.67 ± 0.24 , respectively ($p=0.001$). Similarly, it was able to detect significant difference across PV patients with no lesions, mucocutaneous lesions, skin involvement only and mucosal lesions only ($p<0.001$). Treatments had no impact on EQ-5D-5L index scores at all. Number of comorbidities was associated with greater impairment in EQ-5D index scores ($p<0.001$).

4.5 Healthcare resource utilization and cost of illness in pemphigus

In the 12 months preceding the survey 79.8% of the patients presented on a dermatological outpatient visit, 35.8% on a GP visit and 49.5% were hospitalized due to pemphigus. Overall, 97.2% of our patients received treatment, of which 84.4% had

systemic therapy. Informal care has been provided for 28 patients with the average duration of 5.3 hours per week. Work productivity loss was reported by 20 patients where absenteeism accounted for an average of 304.5 hours per week, presenteeism for 41.1 hours per week.

The average annual cost of pemphigus was 1,235,294 HUF per patient. Direct costs made 42.3% of the total, 522,565 HUF altogether. Direct medical costs accounted for 20.8% of the total costs whereas direct non-medical costs for 21.5%. Indirect costs amounted to 712,729 HUF (58%). Of the direct medical costs, treatment costs (11%) and hospital admission costs (6%) had the greatest cost burden. Informal care was the most significant among direct non-medical costs (235,927 HUF, 19%) exceeding the total sum of inpatient and outpatient care costs. Absenteeism had the greatest burden of indirect costs with 88.1%, presenteeism accounted for 11.9%.

5 Conclusions

- I. Our study was the first to investigate health state and HRQoL of Hungarian pemphigus patients.
 - a. We were the first at an international level to use EQ-5D among pemphigus patients thus measuring health utilities in this population.
 - b. Of the five dimensions of EQ-5D, most patients reported problems in pain/discomfort, least problems were reported in self care.
 - c. We proved the feasibility of EQ-5D and its good convergent validity against a dermatology-specific measure of HRQoL, DLQI and to disease severity measure (ABSIS) and pain scales. With the application of EQ-5D we were able to differentiate across groups of patients based on disease severity, characteristics of symptoms (skin and/or mucous membrane), and comorbidities.
- II. We assessed the costs of pemphigus in Hungary.
 - a. We were the first at an international level to measure indirect costs of pemphigus and the first in Europe to estimate the total costs of disease.
 - b. The cost of pemphigus seems to be considerable from the societal perspective with the greatest cost burden originating from pharmacological therapy, informal care and absenteeism.

6 List of publications

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